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(54) Title: MAGNETIC TARGETED CARRIER COMPOSED OF IRON AND POROUS MATERIALS FOR THE TARGETED DELIVERY OF BIOLOGICALLY ACTIVE AGENTS

(57) Abstract: The invention relates to magnetically responsive compositions comprising iron-ceramic particles used to carry substances for *in vivo* medical diagnosis and/or treatment. The particles are formed by joint deformation of iron and ceramic powders. Diagnostic or therapeutic substances may be adsorbed thereon. The particles may be produced by mechanical milling of a mixture of iron and ceramic powders.

MAGNETIC TARGETED CARRIER COMPOSED OF IRON AND POROUS MATERIALS FOR THE TARGETED DELIVERY OF BIOLOGICALLY ACTIVE AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is the United States national phase of International Patent Application No. PCT/US00/_____, filed October 13, 2000, which claims priority to United States Provisional Application Serial No. 60/160, 293, filed October 18, 1999.

INTRODUCTION

This invention relates to compositions, methods of manufacture and methods for delivery of biocompatible particles to a selected location in a body and, more particularly, relates to particles capable of carrying biologically active compounds and which provide for targeted magnetic transport of the particles and their maintenance in a predetermined place as a localized therapeutic treatment for disease, diagnostic aid, or bifunctional composition capable of acting as both a diagnostic and therapeutic agent.

The site-specific delivery of biologically active agents would enable enhancement of therapeutic activity of chemotherapeutics while minimizing systemic side effects. Magnetic carrier compositions for treating various disorders have been previously suggested and utilized, and include compositions which are guided or controlled in a body in response to an externally applied magnetic field. (See Lieberman *et al.*, U.S. Patent 4,849,209; Schroder *et al.*, U.S. Patent 4,501,726; Chang, U.S. Patent 4,652,257; and Mirell, U.S. Patent 4,690,130).

One such known composition, deliverable by way of intravascular injection, includes microspheres made of a ferromagnetic component covered with a biocompatible polymer (albumin, gelatin, and polysaccharides) which also contains a drug (Driscol, C.F. *et al.*, *Prog. Am. Assoc. Cancer Res.*, 1980, p. 261).

It is possible to produce albumin microspheres up to 3.0 μm in size containing a magnetic material (magnetite Fe_3O_4) and the anti-tumoral antibiotic doxorubicin (Widder, K. *et al.*, *J. Pharm. Sci.*, 68:79-82, 1979). Such microspheres are produced through thermal and/or chemical denaturation of albumin in an emulsion (water-in-oil), with the disperse

phase containing a magnetite suspension in a medicinal solution. A similar technique has been used to produce magnetically controlled, or guided, microcapsules covered with ethylcellulose containing the antibiotic mitomycin-C (Fujimoto, S. *et al.*, *Cancer*, 56: 2404-2410,1985).

Magnetically controlled liposomes, 200 nm to 800 nm in size, capable of carrying preparations that can dissolve atherosclerotic formations are also known. This method is based upon the ability of phospholipids to create closed membrane structures in the presence of water (Gregoriadis G., Ryman B.E., *Biochem. J.*, 124:58, 1971).

Such previously known compositions have not always proven practical and/or effective. Often, there is ineffective drug concentration delivered to the targeted site. Many of the compositions lack adequate transport capacity, exhibit weak magnetic susceptibility, and/or require extremely high flux density magnetic fields for their control. In some cases, there is no real localization of the particles enabling a precise local therapy. Other shortcomings include non-specific binding and toxicity to untargeted organs for compositions incorporating antibodies and peptides, and drug diffusion outside of the desired site for intra-tumoral injection based technologies. Some compositions are difficult to manufacture or prepare consistently, sterilize, and store without changing their designated properties.

Thus, there remains a need for an effective biocompatible composition that is capable of being transported magnetically and that is relatively easy to manufacture, store and use.

One suggested composition comprises ferrocarbon particles for use as magnetically susceptible material for magnetically controlled compositions. These particles have a major dimension (*i.e.*, largest diameter) of about 0.2 µm to about 5.0 µm (and preferably from 0.5 µm to 5.0 µm) and contain from about 1.0% to about 95.0% (by mass) of carbon, with the carbon strongly connected to iron. The particles are obtained by jointly deforming (*i.e.*, milling) a mixture of iron and carbon powders. See U.S. Patents 5,549,915; 5,651,989; 5,705,195 and U.S. Patent Application Serial Nos. 09/003,286, and 09/226,818, which are incorporated herein by reference.

Previous applications of this technology arose from a desire to make alloys that were not achievable through smelting processes. Not all conceivable alloys can be made by smelting, as the solubility of one molten metal in another limits the concentrations that the

mixtures can achieve. Milled ferrocarbon particles were derived as an adaptation of a technique for making alloys. The milling technique is fine tuned to produce a durable connection between the two materials without intimately mixing them as an alloy, which would result in reduction or elimination of both the magnetic moment and/or the drug carrying capacity. The idea of combining iron and carbon by milling arose from their natural mixability, as in the smelting process for forming alloys.

SUMMARY OF THE INVENTION

It has now been found that iron-ceramic particles can be produced by the milling method. This is surprising because alloys using these materials have not previously been demonstrated. Thus, it was not thought that a durable interface between the iron and the ceramic material could be formed.

Iron-ceramic composite particles show great versatility to bind to various drugs that adsorb at the particle surface for easy incorporation of the active agent. Additionally, iron-ceramic particles utilize metallic iron with a higher magnetic susceptibility than iron oxides. thereby facilitating and expediting mobility to the treatment site. Furthermore, the biocompatibility properties of ceramics are well known.

Biocompatible and biodegradable ceramic materials, based on hydroxyapatite and other calcium phosphate derivative materials have been used as bone replacement material in dental and skeletal procedures. However, the concept of magnetically targeting a ceramic material used as a carrier is completely novel. This invention provides a magnetically responsive composition that carries biologically active substances. Generally, iron-ceramic composite particles can be used to target the delivery of a number of biologically active agents, diagnostics, or bifunctional compositions. Methods of production and use thereof are also provided.

The aim of this invention is to improve some parameters of magnetically controlled compositions used for the targeted transport of a biologically active substance, including: enabling use of natural bone constituents in the carrier particle, expanding the categories of therapeutics and diagnostics for which this technology can be used, increasing relative absorption capacity and magnetic susceptibility by, for example, providing a large number of

ionic groups that enable binding of compounds by ionic interactions, improving biocompatibility and biodegradability, intensifying diagnostic and therapeutic effect, simplifying the technology of manufacturing the magnetically controlled composition, and ensuring its guaranteed long-term storage capabilities without changing the desired characteristics.

This is achieved by using suitable composite, iron-ceramic particles, as a magnetically susceptible material for a magnetically controlled composition. The particles are disk and spherically shaped, approximately 0.1 to 10.0 µm in diameter, and contain 1.0% to 95.0% ceramic (or a derivatized ceramic) and 5.0% to 99.0% iron, by iron. They are obtained by jointly deforming (*i.e.*, milling) a mixture of iron and ceramic powders. Adsorption occurs on the surface, or modified surface, of the particle so the drug is readily available and capable of incorporation at the treatment site.

The powders are combined in a planetary ball, or attrition mill with a solvent (*e.g.* ethanol). The resulting composite powder is then sieved or magnetically separated to obtain the desired fraction of product. and correspondingly, the desired magnetic susceptibility. The biologically active agent or diagnostic aid is adsorbed to or deposited on to the composite and administered to the patient in a suspension of the composite in a sterile diluent.

The methods of use include methods for localized *in vivo* diagnosis or treatment of disease providing a magnetically responsive iron-ceramic carrier having adsorbed thereon a biologically active substance selected for its efficacy in diagnosing or treating the disease, and injecting the carrier into the body of a patient. For example, the carrier is injected by inserting delivery means into an artery to within a short distance from a body site to be treated and at a branch or branches (preferably the most immediate) to a network of arteries carrying blood to the site. The carrier is injected through the delivery means into the blood vessel. Just prior to injection, a magnetic field is established exterior to the body and adjacent to the site with sufficient field strength to guide a substantial quantity of the injected carrier to, and retain the substantial quantity of the carrier at, the site. Preferably, the magnetic field is of sufficient strength to draw the carrier into the soft tissue at the site adjacent to the network of vessels, thus avoiding substantial embolization of any of the larger

vessels by the carrier particles. See, for example, U.S. Provisional Application Ser. No. 60/160,293, which is incorporated herein by reference.

It is therefore an object of this invention to provide a highly magnetically responsive composition for optionally carrying biologically active substances and methods of production and use thereof.

It is another object of this invention to provide a magnetically responsive carrier for biologically active substances that has high magnetic responsiveness, yet is durable during storage and use.

It is another object of this invention to provide a magnetically responsive composition comprising particles approximately 0.1 to 10.0 µm in diameter, each iron-ceramic particle containing 1.0% to 95.0% ceramic (or a ceramic derivative) and 5.0% to 99.0% iron, by mass.

It is still another object of this invention to provide a composition utilized for localized *in vivo* diagnosis or treatment of disease including a carrier with composite iron-ceramic particles approximately 0.1 to 10.0 µm in diameter, each iron-ceramic particle containing 1.0% to 95.0% ceramic (or a ceramic derivative) and 5.0% to 99.0% iron, by mass, and having adsorbed thereon one or more optional biologically active substances selected for efficacy in diagnosing and/or treating a particular disease.

With these and other objects in view, which will become apparent to one skilled in the art from the following description, this invention resides in the novel construction, combination, arrangement of parts and methods substantially as hereinafter described, and more particularly defined by the appended claims, it being understood that changes in the precise embodiment of the herein disclosed invention are meant to be included as they come within the scope of the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a magnified photograph (X1000) of composite iron-silica particles.

FIG. 2 is a magnified photograph (X3000) of composite iron-silica particles.

FIG. 3 is a flow diagram of the production process of this invention.

FIG. 4 is a Doxorubicin binding curve for an iron-silica gel composite.

FIG. 5 is Doxorubicin binding curve for an iron-C18 composite.

FIG. 6 is a Scanning Electron Microscopy photograph showing the morphology of iron-hydroxyapatite particles.

FIG. 7 is the same frame as in FIG. 6, with monitoring of backscatter to show iron in white and hydroxyapatite in black.

FIG. 8 is the spectra of the particle shown in FIG. 6 confirming that the white spots are composed of iron.

FIG. 9 is the spectra of the particle shown in FIG. 6 confirming that the black spots are composed of hydroxyapatite.

FIG. 10 is particle size analysis of hydroxyapatite particles using light scattering technique.

FIG.11 is a magnetic susceptibility curve of an iron-hydroxyapatite microparticle using magnetometer technique.

FIG. 12 is a Langmuir isotherm plot for iron-hydroxyapatite.

FIG. 13 is a Langmuir isotherm plot for hydroxyapatite (no iron).

FIG. 14 is a doxorubicin desorption profile for iron-hydroxyapatite.

FIG. 15 shows labeling of iron-hydroxyapatite particles with Indium 111 by direct incubation and stability in different media.

FIG. 16 shows labeling of iron-hydroxyapatite particles with Indium 111/oxyquinoline and stability in different media.

DETAILS OF THE INVENTION

The invention is a composite particle comprised of 1.0% to 95.0% a ceramic (or ceramic derivative) and 5.0% to 99.0% iron, by mass. With compositions having less than 1.0% ceramic, the binding capacity of a particle is decreased to the point of being largely ineffective for carrying biologically active substances. With compositions of greater than 95.0% ceramic, the magnetic susceptibility is generally reduced beyond an effective level for targeting biologically active substances *in vivo*. The particles are disk and spherically shaped, approximately 0.1 to 10.0 µm in diameter.

The term "ceramic" means a natural or synthetic porous, adsorptive material. It is usually, but not necessarily an oxide or mixed oxide, wherein the oxide is metallic or non-metallic. It is usually, but not necessarily inorganic. It is usually, but not necessarily without a crystalline structure. Examples of synthetic ceramic materials include, but are not limited to tricalcium phosphate, hydroxyapatite, aluminum hydroxide, aluminum oxide, aluminum calcium phosphate, dicalcium phosphate dihydrate, tetracalcium phosphate, macroporous triphasic calcium phosphate, calcium carbonates, hematite, bone meal, apatite wollastonite glass ceramics and other ceramic or glass matrices. Also included are polymers that have a degree of crystallinity that will support pores and adsorption. Examples of such polymers include, but are not limited to polyethylenes, polypropylenes, and polystyrenes. Appropriate materials based upon these parameters will be apparanent to any person having ordinary skill in the art. A table of examples follows.

	Oxide	Non-metallic	Amorphous
Silica	Y	Y	Y
Hydroxyapatite	Y	N	Y
Zeolites	Y	N	N
Aluminas	Y	N	Y
Diamond	N	Y	N

Also included in the definition of "ceramic" are silica and silica derivatives (including, but not limited to octadecycl silane [C_{18}], octyl silane [C_8], hexyl silane [C_6], phenyl silane [C_6], butyl silane [C_4], aminopropylsilane [NH_3C_3], cyano nitrile silane [CN], trimethylsilane [C_1], sulfoxyl propyl silane [SO_4C_3], dimethylsilane [C_1], acidic cation-

exchange coating [SCX], basic quaternary ammonium anion exchange coating [SAX], dihydroxypropyl silane [diol]), into a composite particle 0.1 - 10.0 µm in diameter. By way of example, the following silicas are useful for forming the composites of the invention.

Eka Nobel Kromasil®

Packing Material	Particle Shape & Size (µm)	Pore Size (Å)	Pore Volume (ml/g)	Surface Area (m^2/g)	Carbon Load (%)	Phase Type	Bonded Phase Coverage ($\mu mol/m^2$)	End Cap
Kromasil Silica	S,5,7,10, 13,16	100	0.9	340	-	(elemental analysis)		
Kromasil C1	S,5,7,10, 13,16	100	0.9	340	4.7	Monomeric	4.3	-
Kromasil C4	S,5,7,10, 13,16	100	0.9	340	8	Monomeric	3.7	Yes
Kromasil C8	S,5,7,10, 13,16	100	0.9	340	12	Monomeric	3.6	Yes
Kromasil C18	S,5,7,10, 13,16	100	0.9	340	19	Monomeric	3.2	Yes

EM Science

Packing Material	Particle Shape & Size (µm)	Pore Size (Å)	Pore Volume (ml/g)	Surface Area (m^2/g)	Carbon Load (%)	Phase Type	Bonded Phase Coverage ($\mu mol/m^2$)	End Cap
Lichrosorb Si 60	I, 5, 10	60	-	550	0	-	-	No
Lichrosorb Si 100	I, 5, 10	100	-	420	0	-	-	No
Lichrosorb RP-18	I, 5, 10	60	-	150	16.0	Monomeric	1.55	No
Lichrosorb RP- 8	I, 5, 10	60	-	-	9.0	Monomeric	0.78	No
Lichrosorb RP-select B	I, 5, 10	60	0.7	550	12	-	2.5	Yes
Lichrospher Si 60	S, 3, 5, 10	60	0.95	650	0	-	0	No
Lichrospher Si 100	S, 5,10	100	1.25	420	0	-	0	No
Lichrospher RP-8	S, 3, 5, 10	60/100	1.25	350	12.5	-	4.1	No
Lichrospher RP-8 E/C	S, 3,5,10	60/100	1.25	350	13	-	4.2	Yes
Lichrospher RP-18	S, 3, 5, 10	100	1.25	350	21.4	-	3.9	No
Lichrospher RP-18 E/C	S, 3, 5, 10	100	1.25	350	21.5	-	-	Yes
Lichrospher CN	S, 3, 5, 10	100	1.25	350	-	-	-	-
Lichrospher NH2	S, 3, 5, 10	100	1.25	350	4.5	-	3.8	-
Lichrospher Diol	S, 3, 5, 10	100	1.25	350	8.3	-	4.0	-
Lichrospher RP-select B	S, 3, 5, 10	60	0.9	360	12.0	-	3.2	Yes

Packing Material	Particle Shape & Size (μm)	Pore Size (Å)	Pore Volume (ml/g)	Surface Area (m^2/g)	Carbon Load (%)	Phase Type	Bonded Phase Coverage ($\mu mol/m^2$)	End Cap
Inertsil Silica	S, 5	150	-	320	0	-	-	No
Inertsil ODS-2	S, 5	150	-	320	18.5	Monomeric	3.23	Yes
Inertsil ODS-3	S, 3, 5	100	-	450	15	Monomeric	-	-
Inertsil C8	S, 5	150	-	320	10.5	Monomeric	3.27	Yes
Inertsil C8-3	S,5	100	-	450	10	Monomeric	-	Yes
Inertsil Ph (Phenyl)	S, 5	150	-	320	10	Monomeric	2.77	Yes
Inertsil Ph-3 (Phenyl)	S, 5	100	-	450	10	Monomeric	-	Yes
Inertsil C4	S, 5	150	-	320	7.5	Monomeric	3.77	Yes
Inertsil 80Å	S, 5	80	-	450	16	Monomeric	-	Yes
Inertsil Prep ODS, C8,Si	S, 10	100	-	350	14	-	-	-

Vydac/The Separations Group

Packing Material	Particle Shape & Size (µm)	Pore Size (Å)	Pore Volume (ml/g)	Surface Area (m^2/g)	Carbon Load (%)	Phase Type	Bonded Phase Coverage ($\mu mol/m^2$)	End Cap
Vydac 201TP C18	SD, 5, 10	300	0.6	90	8	Polymeric	4.16	Yes
Vydac 218TP C18	SD, 5, 10	300	0.6	90	8	Polyermic	4.16	Yes
Vydac 214TP C4	SD, 5, 10	300	0.6	90	3	Polymeric	4.89	Yes
Vydac 201HS C18	S, 5, 10	80	0.8	450	13.5	-	1.53	-

Waters

Packing Material	Particle Shape & Size (μm)	Pore Size (Å)	Pore Volume (ml/g)	Surface Area (m^2/g)	Carbon Load (%)	Phase Type	Bonded Phase Coverage ($\mu mol/m^2$)	End Cap
μBondapak C18	I, 10	125	1.0	330	10	Monomeric	1.46	Yes
μBondapak Phenyl	I, 10	125	1.0	330	8	-	2.08	Yes
μBondapak NH2	I, 10	125	1.0	330	3.5	-	1.91	No
μBondapak CN	I, 10	125	1.0	330	6	-	2.86	Yes
μPorasil Silica	I, 10	125	1.0	330	-	-	-	No
Novapak C18	S, 4	60	0.3	120	7	-	3.41	Yes
Novapak Phenyl	S, 4	60	0.3	120	5	-	2.34	Yes
Novapak CN	S, 4	60	0.3	120	2	-	1.65	Yes
Novapak Silica	S, 4	60	0.3	120	0	-	0	No
Resolve C18	S, 5, 10	90	0.5	175	10	-	2.76	No
Resolve C8	S, 5, 10	90	0.5	175	5	-	2.58	No
Resolve CN	S, 5, 10	90	0.5	175	3	-	2.53	No
Resolve Silica	S, 5, 10	90	0.5	175	0	-	0	No
Spherisorb Silica	S, 3, 5, 10	80	0.5	220	0	-	0	No
Spherisorb ODS-1	S, 3, 5, 10	80	0.5	220	7	Monomeric	1.47	Partial

Packing Material	Particle Shape & Size (μm)	Pore Size (Å)	Pore Volume (ml/g)	Surface Area (m^2/g)	Carbon Load (%)	Phase Type	Bonded Phase Coverage ($\mu mol/m^2$)	End Cap
Spherisorb ODS-2	S, 3, 5, 10	80	0.5	220	12	Monomeric	2.72	Yes
Spherisorb C8	S, 3, 5, 10	80	0.5	220	6	Monomeric	2.51	Yes
Spherisorb C6	S, 3, 5, 10	80	0.5	220	6	Monomeric	2.27	Yes
Spherisorb Phenyl	S, 3, 5, 10	80	0.5	220	3	Monomeric	1.08	Partial
Spherisorb CN	S, 3, 5, 10	80	0.5	220	3.5	Monomeric	2.37	No
Spherisorb NH2	S, 3, 5, 10	80	0.5	220	2	Monomeric	1.58	No
Spherisorb SAX	S, 5, 10	80	0.5	220	-	-	-	No
Spherisorb SCX	S, 5, 10	80	0.5	220	-	-	-	-
Symmetry	S	100	-	340	19	-	3.09	Yes

YMC

Packing Material	Particle Shape & Size (μm)	Pore Size (Å)	Pore Volume (ml/g)	Surface Area (m^2/g)	Carbon Load (%)	Phase Type	Bonded Phase Coverage ($\mu mol/m^2$)	End Cap
C18-A	S, 3,5,7,10,15 +	120	1.0	~300	17	Monomeric	-	Yes
C18-AM	S, 3,5,7,10,15 +	120	1.0	~300	17	Monomeric	-	Yes
ODS-AQ	S, 3,5,7,10,15 +	120	1.0	~300	16	Monomeric	-	Yes
C8	S, 3,5,7,10,15 +	120	1.0	~300	10	Monomeric	-	Yes
Phenyl	S, 3,5,7,10,15 +	120	1.0	~300	9	Monomeric	-	Yes
C4	S, 3,5,7,10,15 +	120	1.0	~300	7	Monomeric	-	Yes
Basic	S, 3,5,7,10,15 +	-	-	-	-	Monomeric	-	Yes

Note: Bonded phase coverage calculated as per Sander, L.C., and Wise, S.A., *Anal. Chem.*, 56: 504-510, 1984. Material characteristics obtained from literature published by the material manufacturer or an authorized representative thereof.

The powders are mixed in a planetary ball, or attrition mill in the presence of a liquid, for example, ethanol, to inhibit oxidation of the iron. The liquid may also serve as a lubricant during the milling of the iron and ceramic powder, to produce the appropriate particle size distribution. It also may reduce compacting of the ceramic during processing. As a result, the porosity of the ceramic deposits in the composition is maintained so as to maximize adsorption capacity of the particles.

The mixture is put into a standard laboratory planetary ball, or attrition mill of the type used in powder metallurgy. The mill holds canisters containing the iron and ceramic powders, ethanol, and metal or metal alloy balls of various diameters. For example, the mill can have 6 mm diameter balls composed of case hardened metal carbide. An appropriate amount of a liquid (*e.g.*, ethanol), is added for lubrication. Depending on the type used, the mill is run between 2 and 14 hours at speeds of 100 rpm to 1000 rpm. It is believed that mill speeds over 1000 rpm could create an undesirable quantity of overly small particles. Appropriate liquids and milling conditions are easily determined by any person having ordinary skill in the art.

After joint deformation of the iron-ceramic mixture, the particles are removed from the mill and separated from the grinding balls, for example, by a strainer. The particles may be re-suspended in ethanol and homogenized to separate the particles from one another. The ethanol is removed, for example, by rotary evaporation, followed by vacuum drying. Any suitable drying technique may be employed, for example, in a vacuum oven (purging N_2). Particles should be handled so as to protect against oxidation of the iron, for example, in a nitrogen environment.

The resulting dried powder may then be sieved or magnetically separated to obtain the desired fraction of product providing the desired magnetic susceptibility and therapeutic or diagnostic binding capacity. The product is then packaged into dosage units in a nitrogen-purged glove box and terminally sterilized. Any suitable sterilization technique may be employed. For example, the iron-ceramic particles may be sterilized using gamma irradiation and the aqueous solution of excipients may be sterilized by autoclave.

When ready for use, the biologically active agent or agents are adsorbed to or precipitated onto the composite. The composite, with the active agent adsorbed, is administered to the patient in a suspension of the composite in a sterile diluent.

The iron-ceramic particles are useful as a carrier for delivering one or more adsorbed biologically active substances to specific body sites under control of an external magnetic field. As used herein, the term "biologically active substance" includes substances useful for *in vivo* medical diagnosis and/or treatment.

Biologically active substances include, but are not limited to, antineoplastics, blood products, biological response modifiers, anti-fungals, antibiotics, hormones, vitamins, proteins, peptides, enzymes, dyes, anti-allergics, anti-coagulants, circulatory agents, metabolic potentiators, antituberculars, antivirals, antianginals, anti-inflammatories, antiprotozoans, antirheumatics, narcotics, opiates, diagnostic imaging agents, cardiac glycosides, neuromuscular blockers, sedatives, anesthetics, as well as paramagnetic and radioactive particles. Other biologically active substances may include, but are not limited to, monoclonal or other antibodies, natural or synthetic genetic material and prodrugs.

As used herein, the term "genetic material" refers generally to nucleotides and polynucleotides, including nucleic acids, RNA and DNA of either natural or synthetic origin, including recombinant, sense and antisense RNA and DNA. Types of genetic material may include, for example, genes carried on expression vectors, such as plasmids, phagemids, cosmids, yeast artificial chromosomes, and defective (helper) viruses, antisense nucleic acids, both single and double stranded RNA and DNA and analogs thereof. Also included are proteins, peptides and other molecules formed by the expression of genetic material.

For *in vivo* diagnostic imaging, the type of detection instrument available is a major factor in selecting a given radioisotope. The radioisotope chosen must have a type of decay that is detectable for a given type of instrument. Generally, gamma radiation is required. Still another important factor in selecting a radioisotope is that the half-life be long enough so that it is still detectable at the time of maximum uptake by the target, but short enough so that deleterious radiation with respect to the host is minimized. Selection of an appropriate radioisotope would be readily apparent to one having average skill in the art. Radioisotopes which may be employed include, but are not limited to ^{99m}Tc, ^{142}Pr, ^{161}Tb, ^{186}Re, and ^{188}Re. Additionally, typical examples of other diagnostically useful compounds are metallic ions including, but not limited to ^{111}In, ^{97}Ru, ^{67}Ga, ^{68}Ga, ^{72}As, ^{89}Zr, and ^{201}Tl. Furthermore, paramagnetic elements that are particularly useful in magnetic resonance imaging and electron spin resonance techniques include, but are not limited to ^{157}Gd, ^{55}Mn, ^{162}Dy, ^{52}Cr, and ^{56}Fe.

It is also noted that radioisotopes are also useful in radiation therapy techniques. Generally, alpha and beta radiation is considered useful for therapy. Examples of therapeutic compounds include, but are not limited to ^{32}P, ^{186}Re, ^{188}Re, ^{123}I, ^{125}I, ^{90}Y, ^{166}Ho, ^{153}Sm, ^{142}Pr, ^{143}Pr, ^{149}Tb, ^{161}Tb, ^{111}In, ^{77}Br, ^{212}Bi, ^{213}Bi, ^{223}Ra, ^{210}Po, ^{195}Pt, ^{195m}Pt, ^{255}Fm, ^{165}Dy, ^{109}Pd, ^{121}Sn, ^{127}Te, and ^{211}At. The radioisotope generally exists as a radical within a salt, however some tumors and the thyroid may take up iodine directly. The useful diagnostic and therapeutic radioisotopes may be used alone or in combination.

The iron-ceramic composite particle surpasses previous inventions by utilizing metallic iron that has a higher magnetic susceptibility than iron oxides that facilitates and expedites mobility to the treatment site. Advantages over current iron-carbon composite products include surface binding versatility, as well as biocompatibility and biodegradation properties of ceramics that are relatively well known.

As a general principle, the amount of any aqueous soluble biologically active substance adsorbed can be increased by increasing the proportion of ceramic in the particles up to a maximum of about 50% by mass of the composite particles without loss of utility of the particles in the therapeutic treatment regimens described in this application. In many cases it has been observed that an increase in the amount of adsorbed biologically active substance is approximately linear with the increase in ceramic content. However, as ceramic content increases, the susceptibility, or responsiveness, of composite particles to a magnetic field decreases, and thus conditions for their control in the body worsen (although adsorption capacity increases). Therefore, it is necessary to achieve a balance in the iron:ceramic ratio to obtain improved therapeutic or diagnostic results. To increase the amount of agent given during a treatment regimen, a larger dose of particles can be administered to the patient, but the particles cannot be made more magnetic by increasing the dose. Appropriate ratios may be determined by any person having average skill in the art.

It has been determined that the useful range of iron:ceramic ratio for particles intended for use in *in vivo* therapeutic treatments as described in the application is, as a general rule, from about 99:1 to about 5:95 for example about 80:20 to about 60:40. The maximum amount of the biologically active substance that can be adsorbed in the composite iron:ceramic carrier particles of any given concentration of ceramic will also differ depending upon the chemical nature of the biologically active substance, and, in some cases,

the type of ceramic used in the composition. Any person having ordinary skill in the art will be able to determine the proper ratio for the desired application.

Because it is convenient to prepare and market the carrier particles in a dry form, the excipients may be prepared in dry form,and one or more dry excipients are packaged together with a unit dose of the carrier particles. A wide variety of excipients may be used, for example, to enhance adsorption or desorption, or to increase solubility. The type and amount of appropriate dry excipients will be determined by one of skill in the art depending upon the chemical properties of the biologically active substance. Most preferably, the package or kit containing both the dry excipients and dry carrier particles is formulated to be mixed with the contents of a vial containing a unit dose of the drug and sufficient amount of a biologically compatible aqueous solution, such as saline, as recommended by the drug manufacturer, to bring the drug to a pharmaceutically desirable concentration. Upon mixture of the solution containing the dilute drug with the contents of the kit including the dry components (*i.e.*, the dry carrier particles and dry excipients), the drug is allowed to adsorb to the carrier particles, forming a magnetically controllable composition containing a therapeutic amount of the biologically active substance adsorbed to the carrier particles that is suitable for *in vivo* therapeutic or diagnostic use.

Alternatively, a liquid kit may be employed. Here, the carrier particles are contained as one unit, for example, in a vial, while the aforementioned excipients are contained in another unit in the form of an aqueous solution. At the time of administration, the ferroceramic particles are mixed with the contents of a vial containing a unit dose of the drug and sufficient amount of a biologically compatible aqueous solution, such as saline, as recommended by the drug manufacturer, to bring the drug to a pharmaceutically desirable concentration. Subsequently, the resulting particles having the biologically active substance adsorbed thereon, are mixed with yet another unit containing the excipients in aqueous solution. Any suitable sterilization technique may be employed. For example, the ferroceramic particles may be sterilized using gamma irradiation and the aqueous solution of excipients may be sterilized by autoclave. Use of autoclave undesirably oxidizes the ferroceramic particles.

Also, when the biologically active agent to be adsorbed to or deposited onto the microparticles is soluble in an aqueous medium, the buffer used can have an impact on the

overall binding. Any person having ordinary skill in the art would be able to determine the most appropriate buffer.

A diagnostic or therapeutic amount of biologically active substance adsorbed to the carrier particles will be determined by one skilled in the art as that amount necessary to effect diagnosis or treatment of a particular disease or condition, taking into account a variety of factors such as the patient's weight, age, and general health, the diagnostic or therapeutic properties of the drug, and the nature and severity of the disease.

A number of considerations are involved in determining the size of carrier particles to be used for any specific therapeutic situation. The choice of particle size is determined in part by technological constraints inherent in producing the particles under 0.2 μm in size. In addition, for particles less than about 1.0 μm in size, the magnetic control in blood flow and the carrying capacity is reduced. Relatively large particle sizes can tend to cause desirable or undesirable embolization of blood vessels during injection either mechanically or by facilitating clot formation by physiological mechanisms. The dispersion may coagulate, which makes injections more difficult, and the rate at which biologically active substances desorb from the particles in the targeted pathological zones may decrease. The method (such as is described below) of milling together a mixture of iron and ceramic powders produces an irregularly shaped form with a granular surface for the particles, and results in a particle population having an average major dimension of about 0.1 μm to about 5.0 μm.

Because the iron in the particles described in this invention is not in the form of an iron oxide, as is the case in certain previously disclosed magnetically controlled dispersions, the magnetic susceptibility, or responsiveness, of ferroceramic particles is maintained at a high level.

The iron:ceramic particles are characterized by particles of iron and particles of ceramics bound together. The two components are maintained as individual entities. The characteristic substructure of the particles formed during the process of joint deformation of the mechanical mixture of iron and ceramic powders, also increases the magnetic susceptibility of iron inclusions in ferroceramic particles as compared with iron particles having other types of substructure.

Because of the large surface of ceramic deposits in the particles, the adsorbed biologically active substance can comprise about 100% ± 50% by weight, relative to the ceramic fraction of the particle, that being variable from about 5% to 95% of the initial

particle mass, and most preferably from 15% to 60%. In different terms, this can be up to about 200 mg of adsorbed biologically active substance per gram of particles. Therefore, in use, much less of the carrier is injected to achieve a given dose of the biologically active substance or, alternatively, a higher dosage of the biologically active substance per injection is obtained than is the case with some previously known carriers.

The following describes a method for producing small quantities of the ferroceramic composition of this invention, it being understood that other means and mechanisms besides milling could be conceived of for jointly deforming iron and ceramic powders, which comprise the essential starting elements for production of the carrier. The procedure utilized exerts mechanical pressure on a mixture of ceramic and iron particles to deform the iron particles and develop a substantial substructure, which captures the ceramic. The formation of the ferroceramic particles is accomplished without the addition of heat in the process (although the mixture heats up during the mechanical deformation step), and is conducted in the presence of a liquid, for example ethanol, to inhibit oxidation of the iron and to assure that the particles produced are clean (sterile). The liquid may also serve as a lubricant during the milling of the iron and ceramic powder, and may reduce compacting of ceramic during processing. As a result, the density of the ceramic deposits in the composition is maintained so as to maximize adsorption capacity of the particles.

As the joint deformation of the particles and ceramics continues, there develops at the interface of the two solids a third phase comprised of a molecular mixture of iron and ceramic. This interface stabilizes the particle such that it is durable to sterilization and *in vivo* use. This interface is expected to form with other types of ferro particles, such as ferrocarbon, as molecular mixtures of iron and carbon exist in nature or can be formed by smelting, for example, cementite and steel. Ferroceramic mixtures are not commonly known or manufactured such that a molecular mixture may be found at the interface of the two substances.

For example, to produce particles having an average of about 75:25 iron:ceramic ratio by mass, one part of substantially pure iron particles having average diameters from 0.1 μm to 5 μm in size are mixed with about 0.1 to 1.0 parts by weight of substantially pure ceramic granules (typically about 0.1 μm to 5.0 μm in diameter). The iron particles and ceramic granules are mixed vigorously to achieve good distribution throughout the volume. Each biologically active substance should be evaluated individually with the various types of

ceramics in order to determine the optimum reversible ceramic binding. Factors such as pH, temperature, particulate size, salts, solution viscosity and other potentially competing chemicals in solution can influence adsorption capacity, rate, and desorption parameters.

The mixture is put into a standard laboratory planetary ball, or attrition mill of the type used in powder metallurgy. For example, the mill can have 6 mm diameter balls. An appropriate amount of a liquid, for example ethanol, is added for lubrication. The mixture is milled for between 1 and 12 hours, or for the time necessary to produce the particles heretofore described. Depending on the mill used, the speed of the mill may be anywhere in the range from about 100 rpm to about 1000 rpm (typically about 300 rpm.

After joint deformation of the iron:ceramic mixture, the particles are removed from the mill and separated from the grinding balls, for example, by a strainer. The particles may be resuspended in ethanol and homogenized to separate the particles from each other. The ethanol is removed, for example, by rotary evaporation, followed by vacuum drying. Any suitable drying technique may be employed. Particles should be handled so as to protect against oxidation of the iron, for example, in a nitrogen environment.

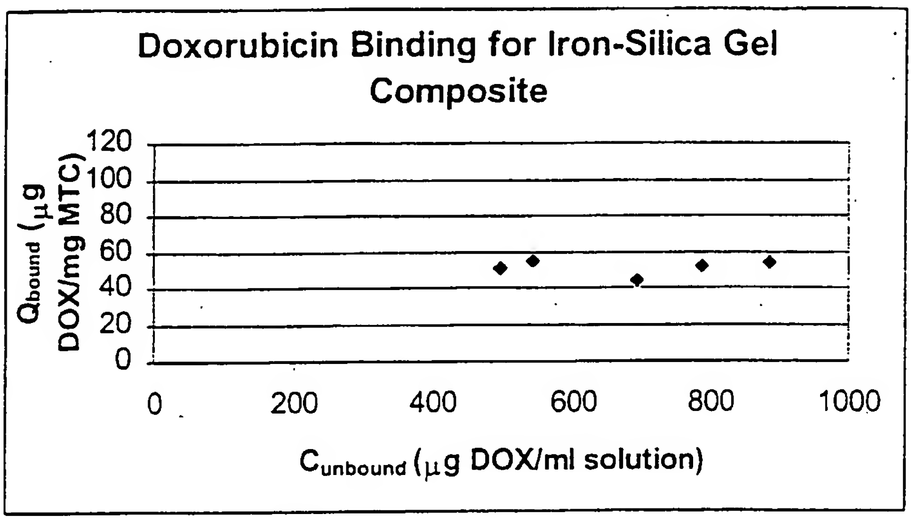
After drying, the particles should be collected according to appropriate size. For example, the particles may be passed through a 20 µm sieve and collected in an air cyclone to remove particles larger than 20 µm. The cyclone only collects particles of a certain size and density, providing a method for removing fines and loose ceramic. The sieved particles may be packaged under nitrogen and stored at room temperature.

Particles may be subaliquoted into dosage units, for example, between 50 and 500 mg per dose, and may be further overlayed with nitrogen, for example. Dosage units may be sealed, for example, with butyl rubber stoppers and aluminum crimps. Dosage units may then be sterilized by appropriate sterilization techniques, for example, gamma irradiation between 2.5 and 4.0 Mrads. Other sterilization techniques may also be used, for example, dry heat and electrobeam sterilization.

When ready for use, or before packaging if the carrier is to be prepared with a preselected biologically active substance already adsorbed thereon, about 50 mg to 150 mg (about 75 mg to about 100 mg is preferred to be absolutely assured of maximum adsorption) of the biologically active substance in solution is added to 1 gram of the carrier. When ready for application to a patient, the combination is placed into suspension (for example, in 5 to 10 ml) of a biologically compatible liquid such as water or saline utilizing normal procedures.

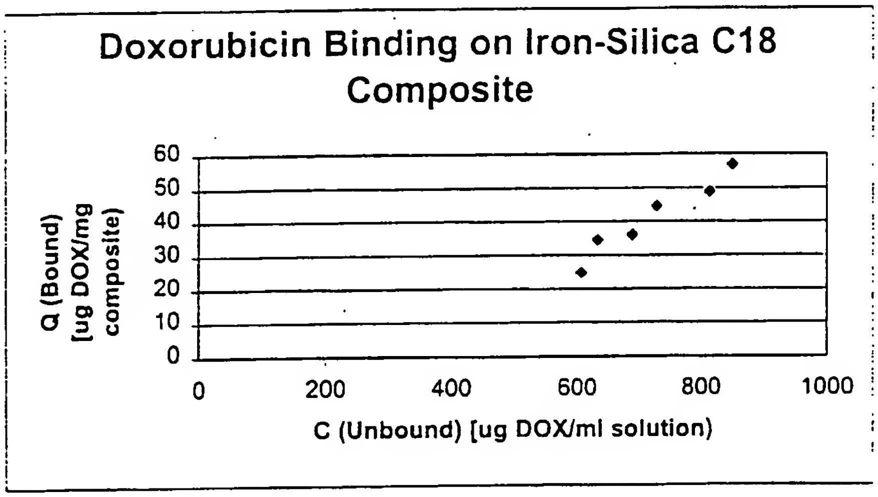
Example 1

A composite particle composed of silica gel and iron was manufactured and preliminary characterization was performed. Characterization included particle sizing analysis (light scattering technique), surface area, pore size analysis, scanning electron microscopy and doxorubicin binding. Tests show that 95% of the final product has particles that are less than 1.11 m and have a mean (volume) diameter of 0.92 m. Results from surface area analysis show the iron-silica gel composite to have a total surface area of 48 m^2/g and a total pore volume of 0.19 cc/g. SEM pictures reveal discrete particles made of both iron and silica gel components (Figures 1 and 2). Preliminary doxorubicin binding assays (Figure 4) show correlation between the concentration of bound (Q) and unbound (C) doxorubicin.



Example 2

A composite particle composed of silica-C18 and iron was manufactured and preliminary characterization was performed. Characterization included particle sizing analysis (light scattering technique) and doxorubicin binding. Tests show that 95% of the final product has particles that are less than 1.60 m and have a mean (volume) diameter of 1.58 m. Preliminary doxorubicin binding assays (Figure 5) show a linear correlation between the concentration of bound (Q) and unbound (C) doxorubicin.



Example 3

In order to bind a biologically active substance for targeted delivery, initially, the structure of the agent would be evaluated. Paclitaxel, for example, contains three -OH groups and three benzene rings. Using the information contained in Table 1, binding would be attempted using those derivatives for benzene rings and -OH groups. First-line silica derivatives would include bare silica, C8 and C18. Second-line derivatives would include phenyl, C1, C2, C4 and C6. Additional silica derivatives would be tested based on the results from experiments. The derivatives should be easily determinable by any person having ordinary skill in the art. Neoplastic agents may be especially useful with the particles of the invention. Examples of other useful neoplastic agents are exemplified in Table 2.

Table 1: Examples of Functional Characteristics of Agents and Silica Derivatives

Functional Characteristics	Potential Silica Derivatives for Binding
-OH groups	Bare silica
Open chain structure	Bare silica
Benzene rings	C8, C18
Long alkanes	C8, C18
Positive charge	Cation exchange (i.e. sulfoxyl (SO_4), carboxyl , SCX)
Negative charge	Anion exchange (i.e. Quartinary (SAX), diethylaminoethyl)
Mixture of rings and –OH groups	Phenyl, C1, C2, C4, C6

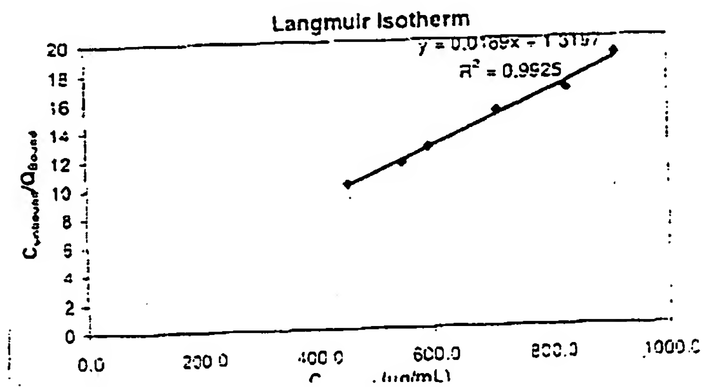
Table 2: Agents Useful in Neoplastic Disease

Agent		Agent Name	Trade Name	Abbr.
ALKYLATING AGENTS	NITROGEN MUSTARDS	Machlorathamine	Mustargen, nitrogen mustard	HN_2
		Cyclophosphamide	Cytoxan, Endoxan	CTX
		Ifosfamide	Ifex	IFS
		Phenylalanine mustard	Melphalan, Alkeran	L-PAM
		Chlorambucil	Lukeran	CLR
	ETHYLENIMINE DERIVATIVES	Triethylenethiophosphoramide	Thiotepa	T-TEPA
	ALKYL SULFONATES	Busulfan	Myleran	MYL
	NITROSOUREAS	Cyclohexyl-choiorethyl nitrosourea	Lomustine, CEENU	CCNU
		1, 3 bis-[2-chloroethyl]-nitrosourea	Carmustine, BiCNU	BCNU
		Streptozotocin	Zanosar	STZC
		Semustine		
	TRIAZENES	Dimethyl triazeno imidazole carboxamide	Dacarbazine	DTIC
ANTIMETABOLITES	FOLIC ACID ANALOGS	Methotraxate	Amethopterin	MTX
	PYRIMIDINE ANALOGS	5-fluoro-2-deoxyuridine	Floxuridine	FUDR
		5-fluorouracil	Cytarabine, Cytosar	5-FU
		Cytosine arabinoside		ARA-C
	PURINE ANALOGS	6-Mercaptopurine	Purinethol	6-MP
		6-Thioguanine	Thioguanine	6-TG
		Deoxycoformycin	Pentostatin	VM-26
NATURAL OR SEMI-SYNTHETIC PRODUCTS	VINCA ALKALOID	Vinblastine	Velban	VLB
		Vincristine	Oncovin	VCR
	ANTIBIOTICS	Doxorubicin	Adriamycin	ADR
		Mitoxantrone	Novantrone	NDV
		Baunorubicin	Daunomycin	DNR
		Bleomycin	Blenoxane	BLEO
		Dactinomycin	Actinomycin D, Cosmegen	---
		Mithramycin	Mithracin	---
		Mitomycin C	Mutamycin	MITO-C, MMC
	TAXANES	Paclitaxel	Taxol	TXL
	ENZYMES	L-asparaginase	Elspar	L-ASP
	EPIPODOPHYLOTOXINS	Etoposide	Vepesid	VP-16
		Teniposide	Vumon	VM-26
MISCELLANEOUS	PLATINUM COORDINATION COMPLEXES	Cis-diamminedichloro-platinum II	Cisplatin, Platinol	CDDP
		Carboulatin	Paraplatin	CBP
	SUBSTITUTED UREA	Hydroxyurea	Hydrea	HXU
	METHYLHYDRAZINE DERIVIATIVE	Procarbazine	Matulane	PROC
	ACRIDINE DERIVATIVE	Amsacrine	Emcyt Amsidyl	m-AM

Agent		Agent Name	Trade Name	Abbr.
HORMONES AND HORMONE INHIBITORS	ESTROGENS	Diethylstilbestrol Conjugated Estrogens Ethinyl Estradiol	 Premarin Estinyl	DES
	ANDROGENS	Testosterone propionate Fluoxymesterone	- - - Halotestin, Ora-Testryl, Utandran	TES
	PROGESTINS	17-Hydroxyprogesterone caproate Medroxyprogesterone acetate Meeestrol acetate	Delalutin Provera Meeace	
	LEUPROLIDE	 Goserelin acetate	Lupron Zoladex	
	ADRENOCORTICOSTEROIDS	Prednisone		
	ANTIESTROGENS	Tamoxifen	Nolvadex	
	HORMONE SYNTHESIS INHIBITORS	Aminoglutethimide	Elipten, Cytadren	
	ANTIANDROGENS	Flutamide	Eulexin	

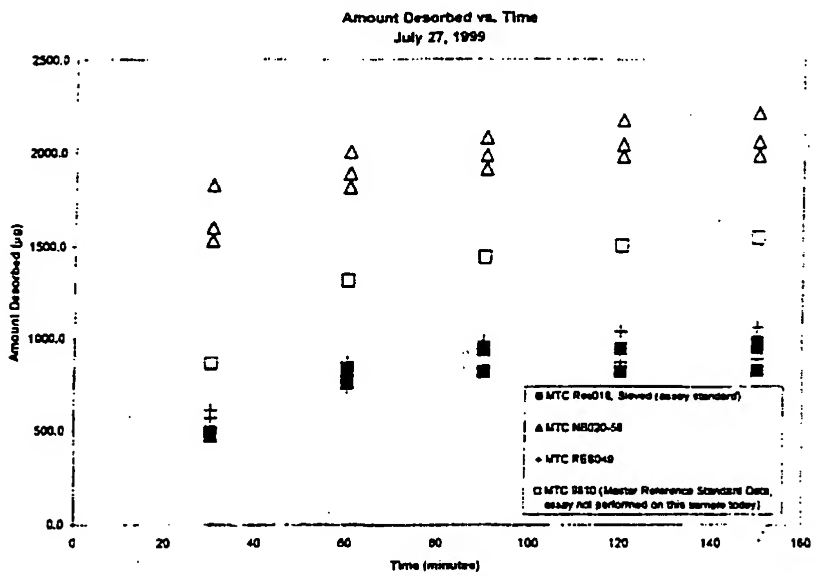
Example 4

The adsorption capacities of hydroxyapatite particles and the iron-hydroxyapatite composite particles were determined by a doxorubicin binding assay. The Langmuir adsorption isotherms were determined from doxorubicin binding data at several concentrations and the total drug loading capacities were calculated from the inverse of the slope of the isotherms. Figure 12 shows the isotherm for the iron-hydroxyapatite composite particles, which had a total capacity of 33 micrograms doxorubicin per milligram particles. Figure 13 shows the isotherm for the hydroxyapatite alone, which has a binding capacity of 53 micrograms doxorubicin per milligram particles. The difference in the drug binding capacity between the hydroxyapatite and the iron-hydroxyapatite composite material is due to the difference in compositions of these samples: the composite material of this example has ~ 25% per weight of hydroxyapatite.



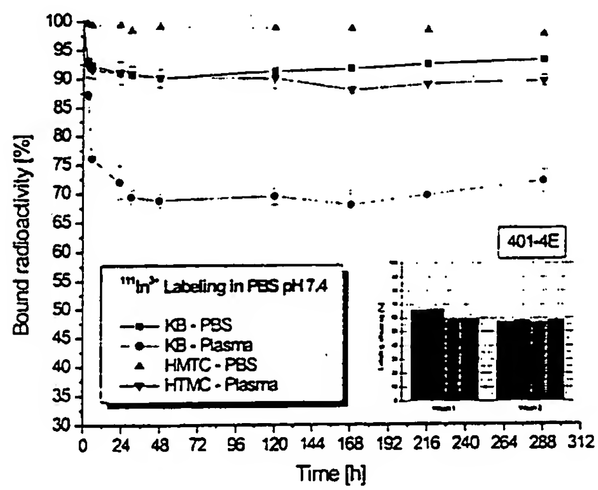
Example 5

Iron-hydroxyapatite composite particles were loaded with doxorubicin by soaking the particles in a concentrated aqueous solution of the drug. The desorption profile was determined in a semi-dynamic assay by measuring the amount of doxorubicin released from the particles incubated in aliquots of human plasma at 37°C. Figure 14 shows that the drug is effectively released from the microparticles as a function of time.



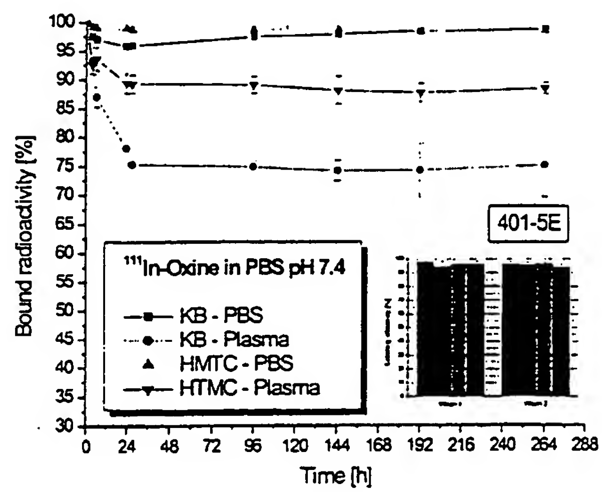
Example 6

Iron-hydroxyapatite micro particles were incubated with Indium-111 in PBS for 30min at 37° C and 1400rpm. The labeling efficiency was determined by comparing the amount of radioactivity in the incubation with the bound radioactivity after two washes with PBS. The inset in Figure 15 shows the resulting labeling efficiencies, which were approximately 60% after the second wash. The stability of the labeled particles was tested in both PBS and human plasma at 37°C. For each time point, the total activity of the sample was compared with the activity in the supernatant, After 12 days, the iron-hydroxyapatite micro particles in PBS retained more than 95% of the Indium-111 and the stability in of the particles in plasma was about 90%. These results demonstrated that the microparticles are easily labeled with Indium cation and that the labeling is very stable in human plasma.



Example 7

The previous experiment was repeated using an Indium complex instead of the Indium salt. Indium-111-oxyquinoline complex was used in the incubation step after being prepared by well know methods. The efficiency and stability were determined as described previously and the results are shown in Figure 16. The labeling efficiency increased to over 90% after the second wash. The stability of the Indium-oxyquinoline labeled micro particles is very similar to the direct labeling, with more than 95% of the radioactivity remaining bound after 12 days in PBS and about 90% of the radioactivity still bound after 12 days in plasma. Thus, Indium complex can also be directly labeled in a very stable manner onto the particles.



What Is Claimed:

1. A magnetically responsive composition comprising particles including iron and ceramic or a derivative thereof, wherein the ratio of ceramic:iron is in the range from about 1% to 95% ceramic to 5% to 99% iron, and wherein the diameter of each particle is approximately 0.1 to 10.0 µm.

2. The composition of claim 1 wherein the ceramic comprises silica.

3. The composition of claim 2, wherein the silica is a macroporous silica gel, having pores in the range from about 2 Å to about 500 Å.

4. The composition of claim 2, wherein the silica is derivatized with octadecylsilane, having pores in the range from about 2 Å to about 500 Å.

5. The composition of claim 1 wherein the ceramic is hydroxyapatite.

6. The composition of claim 5 wherein the hydroxyapatite has pores in the range from about 250 Å to about 1200 Å.

7. The composition of claim 1 wherein the biologically active agent is a selected from the group consisting of chemotherapeutic agents, radioisotopes, genetic materials, contrast agents, dyes, and derivatives or combinations thereof.

8. A kit for administering a biologically active substance to an *in vivo* site in a patient comprising a unit dose of ferroceramic, each particle including a ratio of iron to ceramic in the range from about 99:1 to 5:95.

9. A kit for administering a biologically active substance to an *in vivo* site in a patient comprising a receptacle containing:

    a) unit dose of dry ferroceramic particles, each particle including a ratio of iron to ceramic in the range of about 99:1 to 5:95; and

    b) one or more dry excipients.

10. A kit for administering a biologically active substance to an *in vivo* site in a patient comprising:

    a) a first receptacle comprising a unit dose of ferroceramic particles, each particle including a ratio of iron to ceramic in the range from about 99:1 to 5:95; and

    b) a second receptacle comprising an aqueous solution comprising one or more excipients.

11. The kit of claim 8, 9, or 10, wherein the excipients include a biologically compatible polymer for stabilization after the particles are combined with the aqueous solution.

12. The kit of claim 8, 9, or 10, wherein the excipients include mannitol, sorbitol, sodium carboxy methyl cellulose, polyvinyl pyrrolidone or combinations thereof.

13. The kit of claim 8, 9, or 10, wherein the contents of the kit are combined with a commercially prepared formulation of a biologically active substance.

14. The kit of claim 10 wherein the aqueous solution comprises at least one buffer.

15. The kit of claim 8, 9, or 10, wherein the unit dose of ferroceramic particles has been sterilized by means of gamma irradiation, dry heat or electron beam.

16. The kit of claim 10, wherein the aqueous solution comprising the excipients has been sterilized by means of autoclave.

17. A method of sterilizing a composition comprising iron-silica particles comprising the use of gamma irradiation.

18. A method for localized *in vivo* delivery of a biologically active agent comprising:

a) adsorbing a biologically active agent onto a magnetically responsive carrier composition comprising iron and ceramic;

b) injecting the carrier having the adsorbed biologically active agent into a patient; and

c) establishing a magnetic field exterior to the patient and adjacent to a desired site, wherein the magnetic field is of sufficient strength to guide and retain at the site a portion of the carrier.

19. The method of claim 18 wherein the injecting step is via intra-arterial.

20. The method of claim 18 wherein the desired site is a tumor.

21. The method of claim 18 wherein the biologically active agent is selected from the group consisting of a diagnostic, a therapeutic, a bifunctional and combinations thereof.

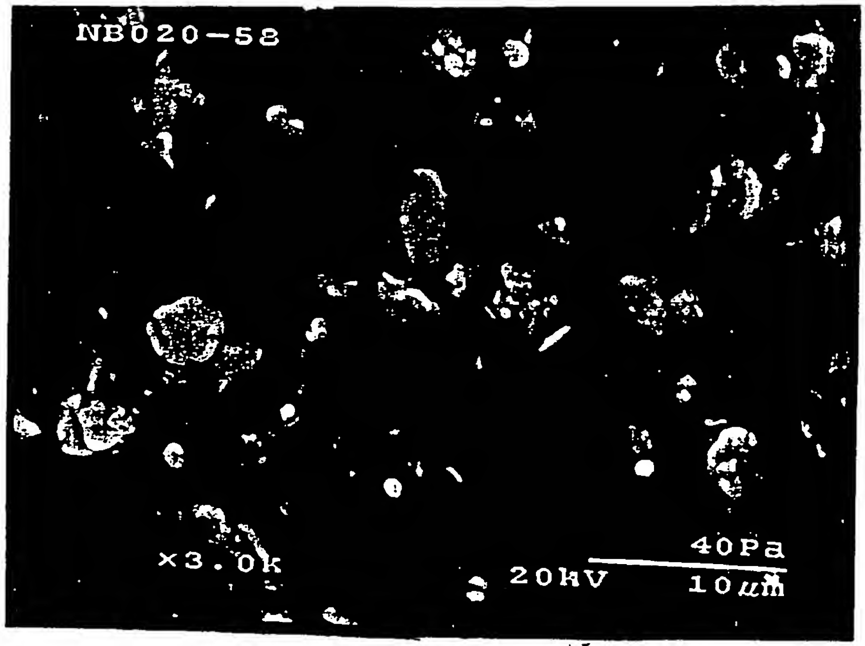


Figure 1

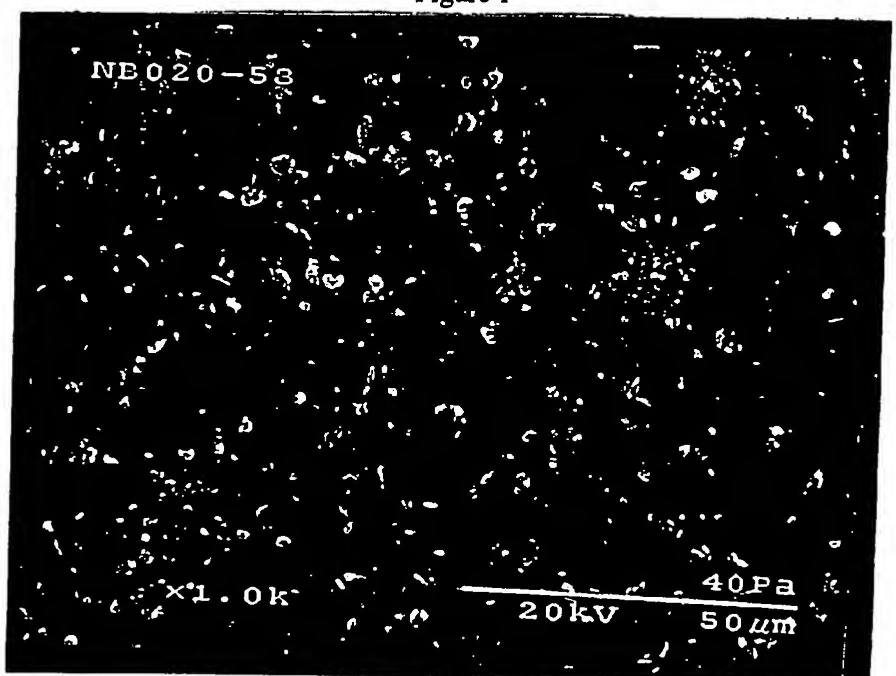


Figure 2

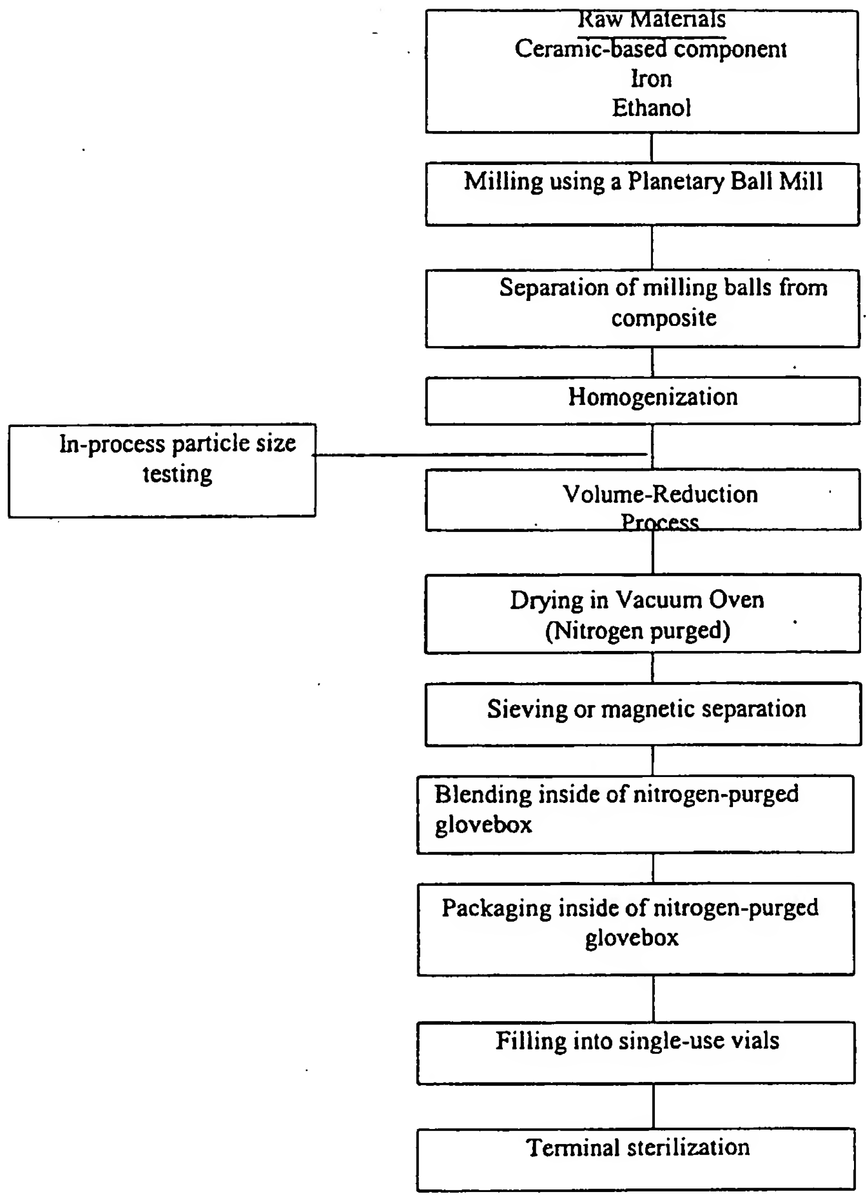

Raw Materials
Ceramic-based component
Iron
Ethanol
Milling using a Planetary Ball Mill
Separation of milling balls from composite
Homogenization
In-process particle size testing
Volume-Reduction Process
Drying in Vacuum Oven (Nitrogen purged)
Sieving or magnetic separation
Blending inside of nitrogen-purged glovebox
Packaging inside of nitrogen-purged glovebox
Filling into single-use vials
Terminal sterilization

Figure 3

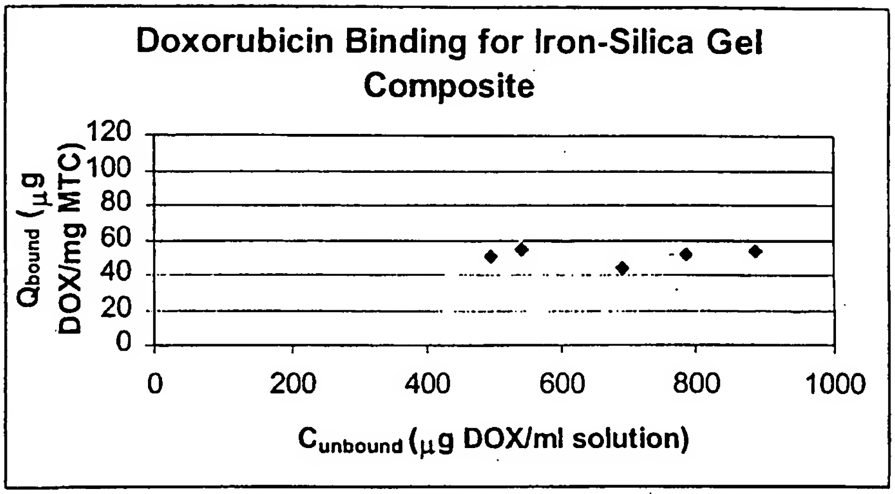


Figure 4

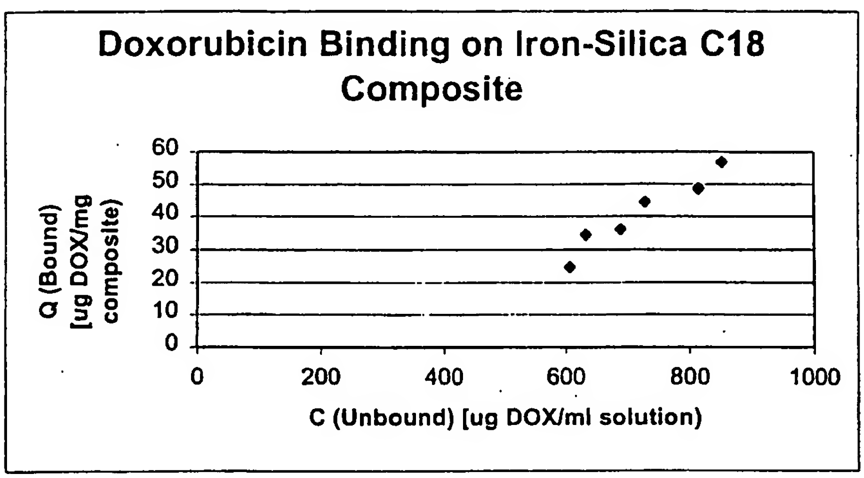


Figure 5

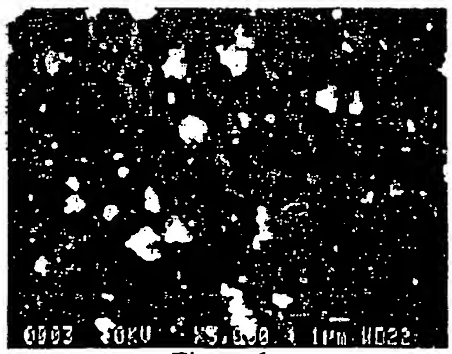


Figure 6

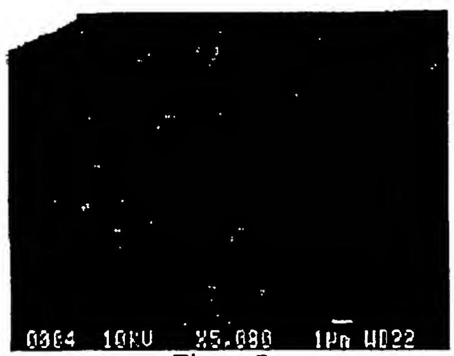


Figure 7

Bright Spots

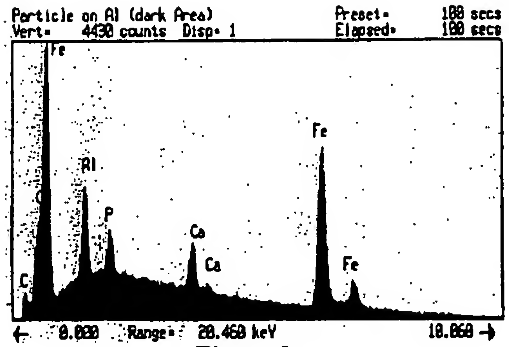


Figure 8

Dark Spots

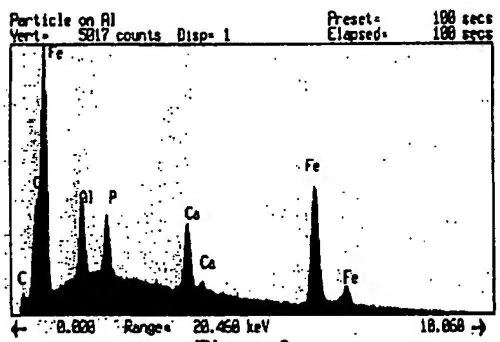


Figure 9

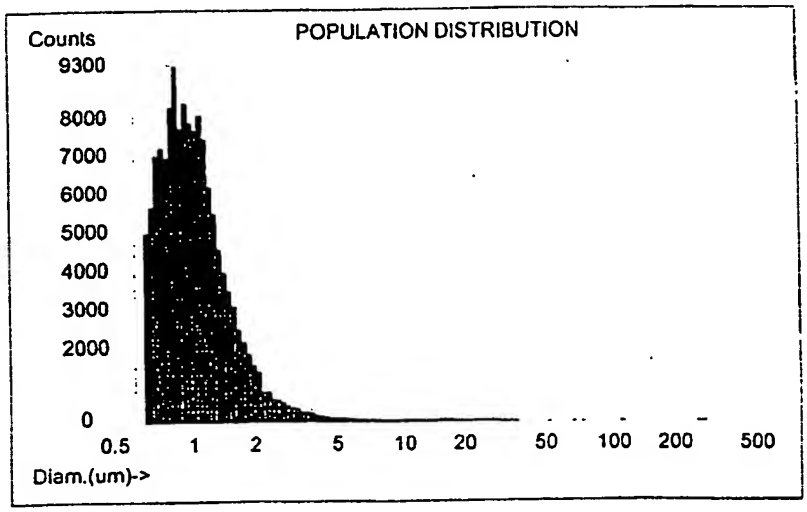


Figure 10

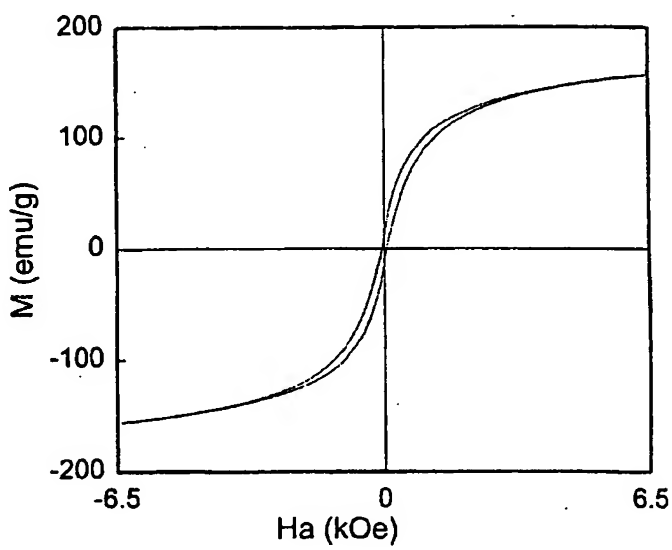


Figure 11

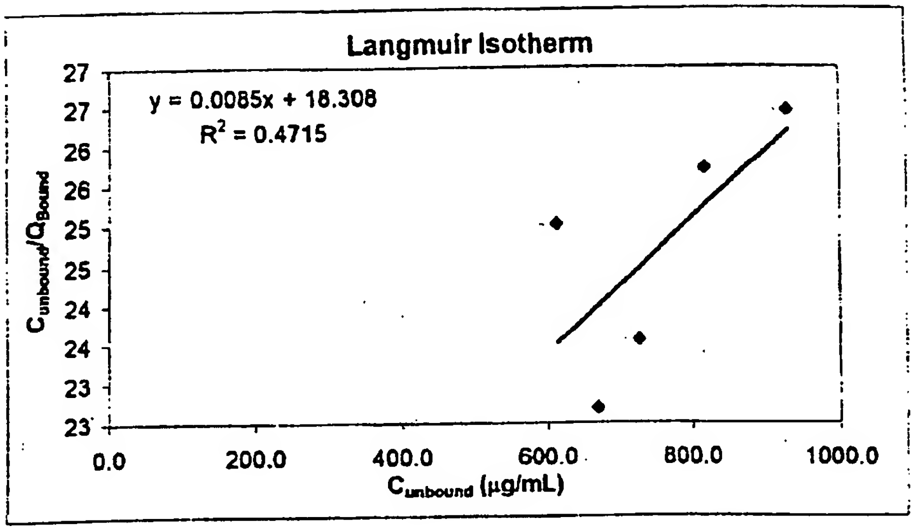


Figure 12

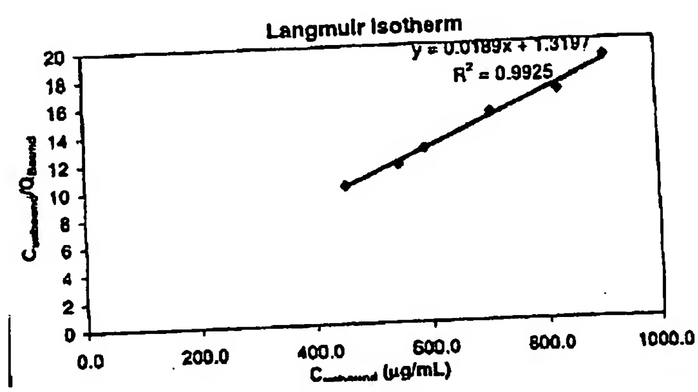


Figure 13

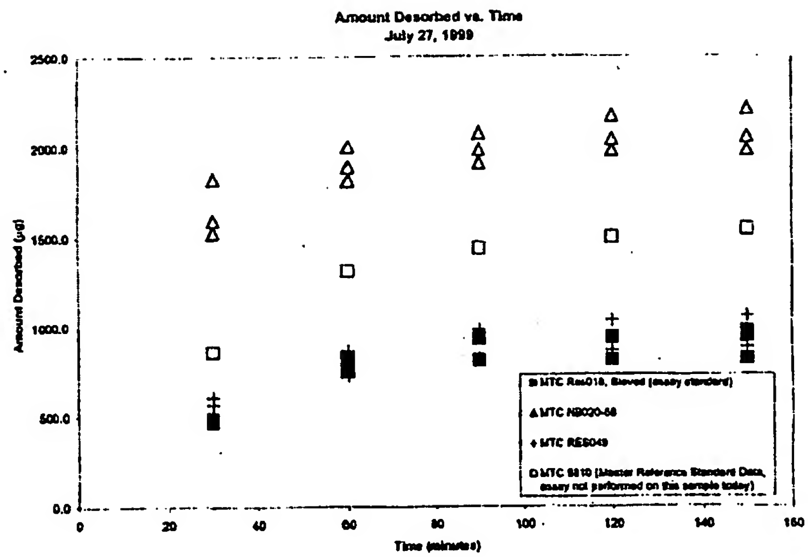


Figure 14

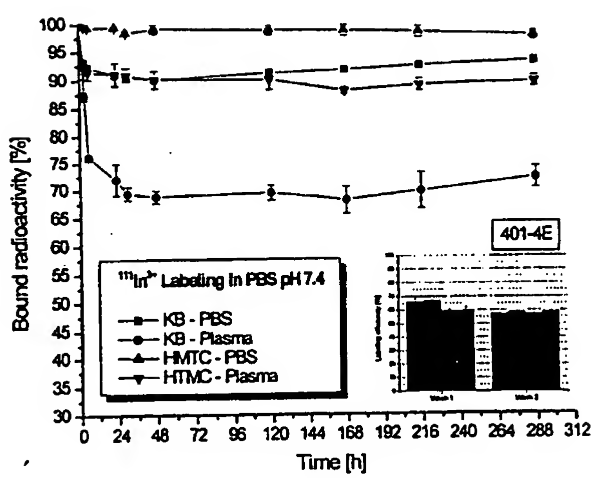


Figure 15

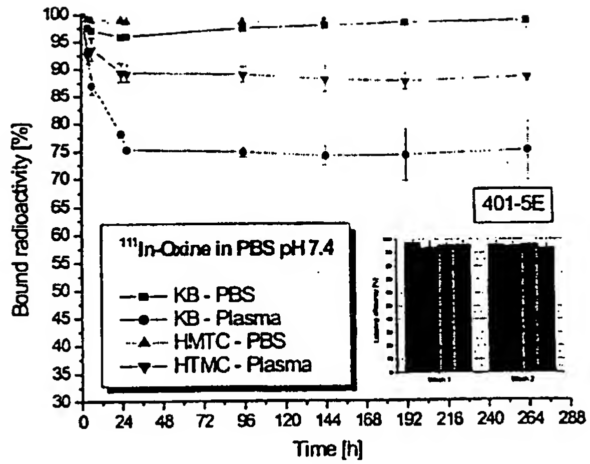

Bound radioactivity [%]
Time [h]
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
0
24
48
72
96
120
144
168
192
216
240
264
288
401-5E
111In-Oxine in PBS pH 7.4
KB - PBS
KB - Plasma
HMTC - PBS
HTMC - Plasma

Figure 16